Cumulative soft drink consumption is associated with insulin resistance in Mexican adults

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ABSTRACT

Background: Insulin resistance (IR) is an important risk factor for type 2 diabetes (T2D) and other cardiometabolic diseases. Recent studies suggest that soft drink consumption could increase IR. However, inconsistent findings have been observed.

Objective: The aim was to estimate the association between the cumulative consumption of soft drinks and IR by means of the HOMA-IR in Mexican adults.

Methods: We analyzed the association between cumulative consumption of soft drinks and HOMA-IR change after 7 y of follow-up in participants ($n = 1073$) of the Health Workers Cohort Study. Soft drink consumption was estimated by food-frequency questionnaires. Insulin was measured by chemiluminescence, and fasting glucose was measured with the enzymatic colorimetric method. HOMA-IR was computed as fasting insulin (mIU/L) × fasting glucose (mmol/L)/22.5. To assess the relation between cumulative soft drink consumption and HOMA-IR change, we performed robust linear regression models. Additionally, we used fixed-effects models to estimate the association between changes in soft drink consumption and change in HOMA-IR.

Results: At baseline, the average age was 44 y. Mean cumulative soft drink consumption was 0.42 servings/d. Median HOMA-IR increased from 1.5 at baseline to 2.0 at follow-up. Soft drink consumption was positively associated with HOMA-IR change. In the multiple linear regression analysis, for each increase in the consumption of 2 (355 mL) soft drinks/d, the average change between baseline and follow-up HOMA-IR showed an increase of 1.11 units (95% CI: 0.74, 1.48).

Conclusions: Our data support the hypothesis that, in Mexican adults, a higher soft drink consumption is associated with an increase in HOMA-IR, despite known risk factors. These findings support the need for reinforcing policies to reduce soft drink consumption in our population. *Am J Clin Nutr* 2020;112:661–668.

Keywords: soft drink, homeostasis model assessment, insulin resistance, Mexican adults, Health Workers Cohort Study

Introduction

Insulin resistance (IR) is defined as a disorder where the sensitivity of tissues to insulin is reduced, leading to metabolic dysfunction (1). IR is an important risk factor for type 2 diabetes (T2D) and a key feature of several noncommunicable diseases, including cardiovascular disease, metabolic syndrome, obesity, and hypertension, among others (2–8).

Over the past decades, sugar-sweetened beverage (SSB) intake, including soft drinks, has progressively increased globally

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Supplemental Table 1 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

The datasets generated during and/or analyzed during the current study are not publicly available due to protecting participant confidentiality, but if required, they can be requested from the corresponding author or from JS.

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Abbreviations used: FE, fixed-effects regression; FFQ, food-frequency questionnaire; HWCS, Health Workers Cohort Study; IMSS, Mexican Social Security Institute; IR, insulin resistance; SSB, sugar-sweetened beverage; T2D, type 2 diabetes.

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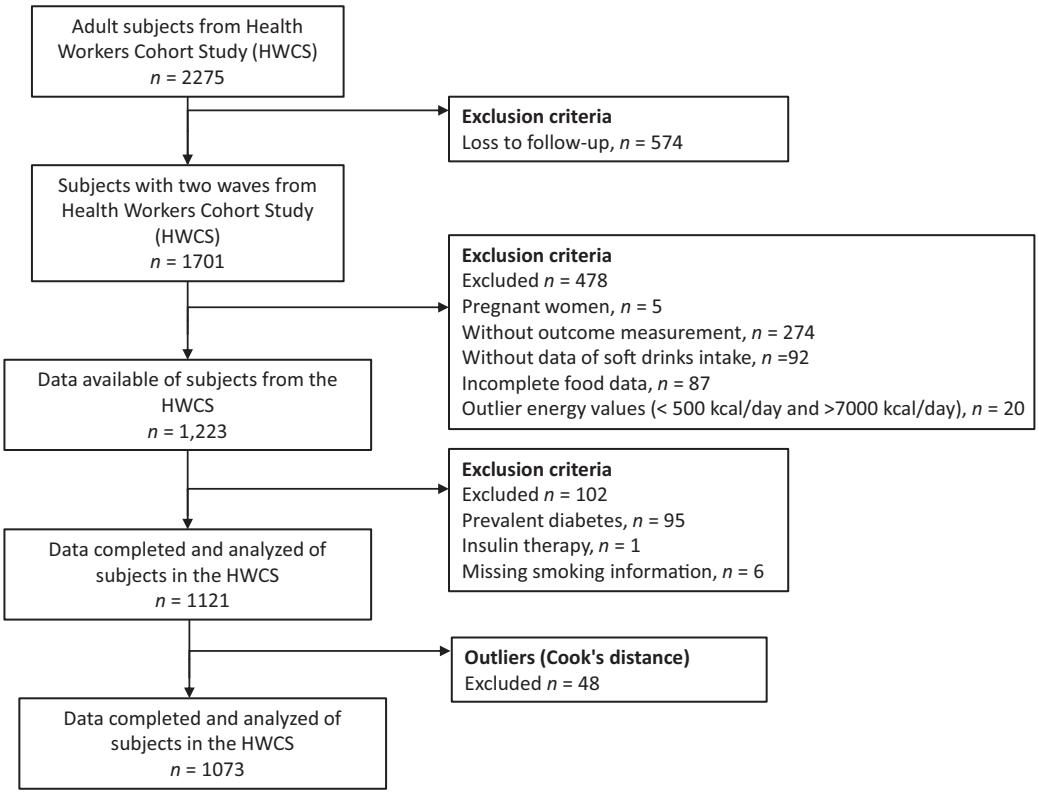

FIGURE 1 Participant flowchart.

(8). For example, in the last 30 y, per capita intake of SSBs increased from 64.4 to 141.7 kcal/d in the United States (9), contributing to a large proportion of the added sugars consumed in the country (10, 11). Similar patterns have been observed in Mexico, where according to the Mexican National Health and Nutrition Survey 2012, the average consumption of soft drinks provided ∼207 kcal/d (12). Furthermore, it has been reported that SSBs contribute 74% of the added sugar intake, being the leading source of added sugars in the Mexican adult population (13).

Previous studies have linked the increasing intake of SSBs to the present epidemic of obesity, T2D, and cardiovascular disease (8, 14–17). However, little is known about the relation between SSB intake and the progression of IR in adults. Short-term randomized clinical trials have observed that high intakes of fructose (18, 19) or sucrose (20) seem to decrease insulin sensitivity, yet other studies failed to demonstrate such a relation (21, 22). Mixed results have also been observed in observational studies evaluating the usual intake of different sugar resources and HOMA-IR in adults (23–26). Short-term studies have pointed at a potential disturbance in HOMA-IR as a result of SSB consumption, yet long-term studies are lacking and are needed to provide information about the impact of cumulative exposure to sugar consumption.

We aimed to evaluate the effect of the cumulative consumption of soft drinks in the change in HOMA-IR in a cohort of Mexican adults. We hypothesized that higher consumption of soft drinks is associated with changes in the levels of HOMA-IR. To assess this hypothesis, we evaluated the cumulative consumption of soft drinks and the change in HOMA-IR levels in a Mexican adult population.

Methods

Study population

The Health Workers Cohort Study (HWCS) is a longitudinal cohort designed to study lifestyles and chronic diseases among individuals living in Morelos, Mexico. Details of the study design cohort characteristics have been previously reported (27). Briefly, the study included 10,729 participants aged between 6 and 94 y who were recruited from 3 different health and academic institutions from 2004 to 2006. For the second wave in 2010–2012, only employees and their relatives from the Mexican Social Security Institute (IMSS; by its Spanish acronym) were invited to participate ($n = 2500$). In this analysis, we included data from 1701 individuals, aged 20–70 y, who successfully completed the 2010–2012 follow-up (77% response rate). We excluded participants <19 y and those >70 y ($n = 210$) and those with missing data on HOMA-IR ($n = 274$) or soft drink consumption ($n = 92$); we also excluded pregnant women ($n = 5$) or subjects undergoing insulin therapy ($n = 1$). In addition, we excluded individuals with missing data on the food-frequency questionnaire (FFQ; those who answered <75% of the questionnaire or who had missing data in an entire section of the questionnaire; $n = 87$) or with implausible energy consumption estimated through a generalized extreme studentized deviate test ($n = 20$; <500

TABLE 1 Descriptive characteristics of the Health Workers Cohort Study[1]

Characteristics	Baseline	Follow-up	*P*
Age,[2] y	44.3 (11.4)	51.4 (11.4)	
Level of education, %			
Primary (from first to sixth grade)	9.5	—	
Secondary (seventh to ninth grade)	16.7	—	
High school (tenth to eleventh grade)	25.2	—	
University or more	47.4	—	
Soft drink consumption,[2,3] servings/d	0.50 (0.60), 5.5	0.42 (0.52), 3.5	<0.001
Cumulative soft drink consumption (throughout the period)[2,3]	—	1022.7 (1277.7), 9712.95	
Cumulative soft drink consumption,[2,3] servings/d	—	0.48 (0.52), 4.0	
Diet soft drinks consumption,[2,3] servings/d	0.07 (0.27), 2.5	0.06 (0.26), 2.5	0.3925
Cumulative diet soda consumption (throughout the period)[2,3]	—	175.9 (613.5), 6577.5	
Cumulative diet soda consumption,[2,3] servings/d	—	0.07 (0.23), 2.5	
Sugar-sweetened beverages,[2,3] servings/d	1.03 (1.5), 6	1.11 (1.5), 12	0.1212
Cumulative flavored water consumption (throughout the period)[2,3]	—	2651.5 (3121.3), 17,147.8	
Cumulative flavored water consumption,[2,3] servings/d	—	1.07 (1.25), 6.5	
Energy intake,[4] kcal/d	1981 (1531–2575)	1739 (1333–2271)	<0.001
Carbohydrate intake,[4] % energy	61 (56–66)	66 (60–72)	<0.001
Insulin,[4] μU/mL	7.4 (2.6–13.5)	8.7 (4.5–14.3)	<0.001
Fasting glucose,[4] mmol/L	4.9 (4.6–5.3)	5.3 (5.0–5.7)	<0.001
HOMA-IR[4]	1.6 (0.5–3.1)	2.1 (1.0–3.6)	<0.001
BMI,[2] kg/m2	26.1 (4.0)	26.8 (4.3)	<0.001
Overweight, %	42.3	44.3	0.0599
Obesity, %	15.4	19.0	0.0003
Physical activity,[4] h/wk	1.5 (0.4–4.1)	1.5 (0.4–3.5)	0.0816
Active (≥150 min/wk), %	37.7	35.0	0.1252
Smoking, %			
Never	58.1	52.5	<0.001
Past	24.7	33.0	<0.001
Current	17.2	11.6	<0.001
Alcohol consumption,[4] g/d	1.0 (0.2–4.0)	0.8 (0.2–3.1)	0.0003
Family history of diabetes, %			
Yes	49.6	59.7	<0.001
Unknown	6.3	5.3	0.3584
Type 2 diabetes, %	—	7.0	

[1] $n = 1073$. *P* values were derived from paired-samples *t* test or Wilcoxon rank-sum test (continuous variables) or McNemar's test (categorical variables).
[2] Values are means (SD).
[3] Values are the difference from maximum - minimum.
[4] Values are medians (25th–75th percentile).

kcal/d or >7000 kcal/d) (28, 29). Also, we excluded individuals with previously diagnosed diabetes at baseline ($n = 95$) or missing smoking information ($n = 9$). Additionally, observations with a Cook's distance of >4 times the mean ($n = 48$) were excluded. The final sample for this analysis consisted of 1073 participants (**Figure 1**). The present study was developed and performed according to the Declaration of Helsinki guidelines. The Research, Ethics, and Biosecurity Committee at the IMSS evaluated and accepted the study protocol and informed-consent forms. In addition, we obtained written informed consent from all participants.

Data collection and blood sample collection

Assessments of IR: HOMA-IR.

Insulin was measured by chemiluminescence (Acces2; Beckman Coulter) and fasting glucose was measured with the enzymatic colorimetric method with a Selectra XL instrument (27). HOMA-IR was computed at each wave using a mathematical formula as follows: HOMA-IR = [fasting insulin (mIU/L) × fasting glucose (mmol/L)]/22.5 (30).

Assessment of cumulative soft drink, diet soda, and flavored water consumption.

Dietary intakes were measured using a 116-item semi-quantitative FFQ derived from an FFQ previously validated in Mexican population (28, 31). Questionnaires inquired about the average frequency of consumption of food and beverages over the past year using standard units or portions. We converted the frequency of consumption of soft drinks (cola and flavored sodas), diet soda, and flavored water (flavored sweetened water, bottled or homemade) to servings per day (standard drink serving of 355 mL). To estimate the cumulative soft drink consumption, we used the formula: (soft drinks at baseline × time) + [(Δ soft drinks × time)/2] (32), where time represents the days that each subject contributed to the cohort and Δ represents

TABLE 2 Association between soft drink consumption and changes in HOMA-IR, glucose concentrations, and insulin concentrations[1]

	Model 1		Model 2		Model 3	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
HOMA-IR change ($n = 1073$)						
Cumulative soft drink consumption[2]	0.39 (0.17,0.63)	0.001	0.34 (0.11,0.58)	0.004	0.34 (0.11–0.58)	0.004
Soft drinks [3]	− 0.003 (−0.23, 0.22)	0.982	− 0.02 (−0.25, 0.21)	0.863	− 0.06 (−0.30, 0.18)	0.642
Time[3]	− 0.06 (−0.13, 0.01)	0.113	− 0.05 (−0.12, 0.02)	0.178	− 0.04 (−0.12, 0.03)	0.216
Soft drinks × time[3]	0.06 (0.03, 0.09)	<0.001	0.05 (0.01, 0.08)	0.005	0.05 (0.01, 0.08)	0.005
Glucose concentration change ($n = 1092$)						
Cumulative soft drink consumption[2]	2.23 (1.04, 3.43)	<0.001	2.41 (1.14, 3.68)	<0.001	2.41 (1.14, 3.68)	<0.001
Soft drinks [3]	− 0.95 (−2.00, 0.10)	0.076	− 1.21 (−2.29, −0.14)	0.027	− 1.21 (−2.29, −0.14)	0.031
Time[3]	0.63 (0.24, 1.03)	0.002	0.61 (0.21, 1.00)	0.003	0.61 (0.21, 1.00)	0.003
Soft drinks × time[3]	0.36 (0.19,0.53)	<0.001	0.38 (0.20,0.56)	<0.001	0.38 (0.20,0.56)	<0.001
Insulin concentration change ($n = 1078$)						
Cumulative soft drink consumption[2]	1.21 (0.29, 2.13)	0.01	0.86 (−0.09, 1.82)	0.076	0.89 (−0.05, 1.84)	0.064
Soft drinks [3]	0.57 (−0.26, 1.40)	0.178	0.6 (−0.24, 1.45)	0.160	0.51 (−0.37, 1.39)	0.257
Time[3]	− 0.32 (−0.61, −0.04)	0.025	− 0.28 (−0.57, 0.004)	0.053	− 0.27 (−0.55, 0.01)	0.062
Soft drinks × time[3]	0.18 (0.06, 0.31)	0.004	0.13 (−0.001,0.26)	0.053	0.13 (−0.002, 0.26)	0.053

[1]Model 1 included as additional predictors: initial age, sex, smoking status, initial educational level, alcohol consumption, physical activity, and family history of diabetes. Variables that remained constant through time were included as interactions with time in the fixed-effects regression model (i.e., initial age, initial educational level, and sex). Model 2 included as additional predictors those from model 1 except for family history of diabetes, which was replaced for 3 dietary patterns. Model 3 included the additional predictors from model 2 plus adjustment for energy intake.

[2]Robust regression: The outcome variable was specified as a change from initial to final measurement with cumulative soft drink consumption as the main predictor. The information of each subject was summarized in 1 observation.

[3]Fixed-effects regression: The outcome variable and predictors were specified as deviations from their subject-specific means across measurements. Each subject contributed with 2 observations.

the difference between soft drink consumption at follow-up and baseline measurements (**Supplemental Figure 1**). The cumulative consumption of diet soda and flavored water was estimated following a similar procedure as for soft drinks.

Assessment of covariates.

Baseline and follow-up questionnaires inquired about demographic characteristics, such as age and gender, family history of diabetes, educational level, and lifestyle habits, such as smoking status, alcohol intake, and physical activity (27). We assessed leisure-time physical activity by asking participants to report the frequency, intensity, and duration of recreational physical activity in the previous year (27, 33). Leisure-time physical activity was categorized as active (≥150 min/wk) and inactive (<150 min/wk). Smoking status was categorized as never smoker, former smoker, or current smoker. Educational level was categorized as primary (from first to sixth grade), secondary (seventh to ninth grade), high school (tenth to eleventh grade), university or more. BMI was calculated from weight and height (kg/m^2) and was categorized as normal weight (BMI <25.0), overweight (BMI: 25.0 to <30.0), and obesity (BMI ≥30.0). T2D was defined with ≥1 of the following 3 criteria: self-report of physician-diagnosed diabetes, use of hypoglycemic medication (including insulin) or fasting glucose >126.0 mg/dL.

TABLE 3 Association between soft drink consumption categories and HOMA-IR change (sensitivity analysis)[1]

	Model 1		Model 2		Model 3	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Soft drinks[2]						
<1 serving/wk ($n = 262$)	Ref		Ref		Ref	
1–4 servings/wk ($n = 571$)	0.34 (0.09, −0.60)	0.011	0.28 (0.02, 0.55)	0.036	0.28 (0.01, 0.47)	0.041
≥5 servings/wk ($n = 240$)	0.25 (−0.13, 0.65)	0.197	0.17 (−0.24, 0.57)	0.423	0.13 (−0.28, 0.54)	0.533
Time[3]	− 0.07 (−0.15, 0.01)	0.074	− 0.06 (−0.14, 0.02)	0.119	− 0.06 (−0.13, 0.02)	0.147
Soft drinks × time[3]						
<1 serving/wk	Ref		Ref		Ref	
1–4 servings/wk	0.05 (−0.003, 0.10)	0.065	0.05 (−0.007, 0.10)	0.090	0.05 (−0.008, 0.10)	0.092
≥5 servings/wk	0.08 (0.01, 0.14)	0.018	0.06 (−0.0007, 0.13)	0.053	0.06 (−0.001, 0.13)	0.053

[1]Model 1: Adjusted for baseline age (years), sex, smoking, educational level, alcohol, physical activity, and family history of diabetes. Model 2: Additional adjustment for dietary patterns (3 factors) instead of family history of diabetes. Model 3: Model 2 plus adjustment for energy intake. Ref, reference.

[2]Values are from fixed-effects regression.

[3]Values are from Individual-level fixed-effects models.

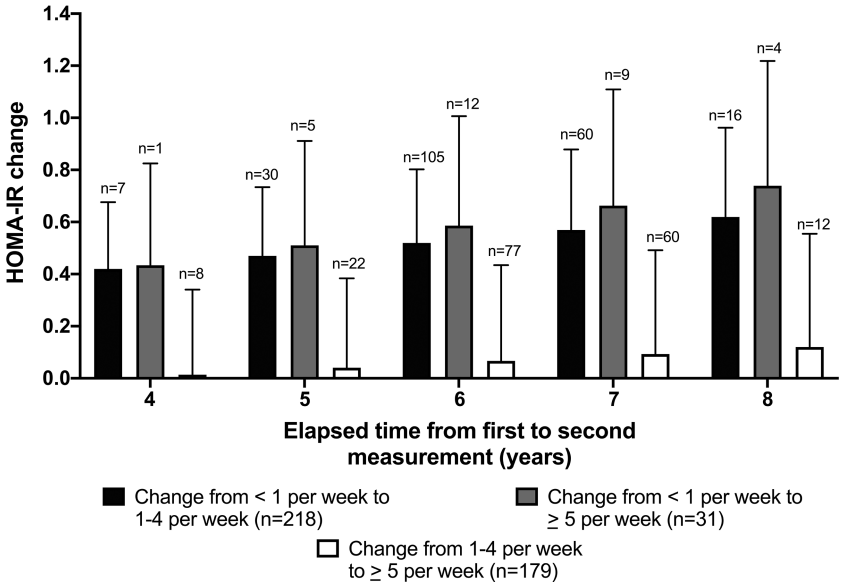

FIGURE 2 Marginal effects of HOMA-IR by soft drink consumption categories. Marginal effects obtained from the fixed-effects model 1 of Table 3 are shown. The sample comprised a total of 1073 subjects who showed variation in HOMA-IR across repeated measurements. The number of individuals who changed from category of soft drink consumption is denoted by "n." Errors bars represent 95% CIs.

Statistical analysis.

Descriptive data are presented as means and SDs, medians and IQR (25th–75th percentile), or proportions (depending on the measurement scale of the corresponding variable) for baseline and follow-up assessments. Differences between study stages were analyzed with the Wilcoxon rank-sum test or paired *t* test for continuous variables and McNemar's test for categorical variables.

To estimate the relation between soft drink consumption and HOMA-IR change, we used 2 modeling approaches. First, we performed a robust linear regression with change in HOMA-IR as a dependent variable and cumulative soft drink consumption as a main predictor. To facilitate the interpretation of the model, we scaled the cumulative consumption variable during the period as a portion of cumulative consumption per day; this was done by dividing the cumulative consumption by the time each individual contributed to the cohort (days). To evaluate the model fit, we examined the normality of residuals, homoscedasticity, and linearity of associations. After reviewing the literature (23, 34) to identify confounders, the following confounding variables were considered. In model 1, we adjusted by baseline age (years), sex, smoking, educational level, alcohol, physical activity, and family history of diabetes. The second model added dietary patterns (3 factors) instead of family history of diabetes. Finally, the third model included model 2 plus adjustments for energy intake (kilocalories per day) (23). In the second approach, fixed-effects regressions (FEs) were used to estimate the association over time, adjusting for several covariates. FE models analyze within-person change while eliminating time-invariant confounding (between-individual differences); thus, these models were used to estimate the association between intraindividual changes caloric and noncaloric drink consumption and changes in HOMA-IR (35). To capture HOMA-IR trajectories over time, because individuals had different time contributions to the cohort, we explored the interaction between time (years) and soft drink consumption (portions per day). This model was adjusted for sex × time, age × time, smoking, educational level × time, alcohol, physical activity, and family history of diabetes. Additionally, we evaluated the association between soft drink consumption, changes in glucose concentrations, and changes in insulin concentrations using the 2 statistical approaches previously mentioned. For the glucose and insulin models, individuals with a Cook's distance of >4 times the mean were excluded, and the model assumptions were evaluated.

In addition, we performed some sensitivity analyses including the following: *1*) analysis of soft drink consumption by consumption categories (<1 serving/wk, 1–4 servings/wk, and ≥5 servings/wk) for the second approach, *2*) exclusion of individuals with incident diabetes or glucose intolerance for both approaches, and *3*) evaluation of the effect of noncaloric beverages or flavored water for the second approach. The marginal effects of the FE model for the change in HOMA-IR by categories of soft drink consumption per year were graphically represented. All statistical analyses were performed using STATA software, version 14.0 (StataCorp).

Results

The final analysis included a total of 1073 individuals with a mean time between baseline and follow-up assessments of 6.7 y. At baseline, the mean age was 44 years (SD = 11.4) and 47% had a high educational level (**Table 1**). The mean cumulative soft drink consumption was 1022.7 servings throughout the period (SD = 1277.7), which is equivalent to consuming 0.42 (SD = 0.52) servings/d; the mean cumulative diet soda consumption was 175.9 servings throughout the period (SD = 613.5), and the mean cumulative flavored water consumption was 2651.5 servings/y (SD = 3121.3). The median HOMA-IR increased

TABLE 4 Average difference in HOMA-IR in selected values of cumulative soft drink consumption per day[1]

Cumulative daily soft drink consumption	HOMA-IR change (95% CI) [2]
0 servings	0.31 (0.15, 0.47)
0.5 servings (177.5 mL)	0.51 (0.39,0.64)
1 serving (355 mL)	0.71 (0.53, 0.89)
1.5 servings (532.5 mL)	0.91 (0.61,1.21)
2 servings (710 mL)	1.11 (0.74, 1.48)

[1] $n = 1073$. 0 servings/d, $n = 24$; >0–0.5 servings/d, $n = 713$; >0.5–1 serving/d, $n = 130$; >1–1.5 servings/d, $n = 81$; and >1.5 servings/d, $n = 125$.

[2] HOMA-IR changes were estimated from a linear regression model.

from 1.6 at baseline to 2.1 at follow-up. At baseline, 42.3% of the sample was overweight and 15.4% were obese; at follow-up, these percentages increased to 44.3% and 19.0%, respectively.

Soft drink consumption was positively associated with the HOMA-IR change (**Table 2**). For the intraindividual effect of the interaction between soft drinks and time, we observed that an increase in 1 serving of soft drink consumption per day was associated with an increase in HOMA-IR of 0.05 units per year of exposure (95% CI: 0.01, 0.08).

Due to the low consumption of soft drinks in the study sample, we explored whether the association was maintained by categories of soft drink consumption. Only 4.9% of the individuals were nonconsumers of soft drinks; therefore, we decided to collapse these into the category of <1 serving/wk. In model 3, we observed that, in individuals with a consumption of ≥5 servings/wk, the change in HOMA-IR over time was higher compared with individuals who consumed <1 serving/wk of soft drinks ($\beta = 0.06$; 95% CI: −0.001, 0.13; $P = 0.053$) (**Table 3**, **Figure 2**).

Sensitivity analyses showed that the association of soft drink consumption and time with HOMA-IR change remained statistically significant despite the exclusion of individuals with incident diabetes ($\beta = 0.05$; 95% CI: 0.02, 0.08) or impaired glucose tolerance during follow-up ($\beta = 0.04$; 95% CI: 0.01, 0.08). In addition, we explored the association between diet soda ($\beta = 0.003$; 95% CI: −0.08, 0.08) and soft drinks + diet soda ($\beta = 0.04$; 95% CI: −0.01, 0.08) in HOMA-IR change; however, the results were not statistically significant (**Supplemental Table 1**).

Table 4 shows the average change in HOMA-IR for different categories of cumulative soft drink consumption. It was observed that the average change in HOMA-IR between the initial and final measurement was greater in those individuals with a higher cumulative consumption of soft drinks per day. For example, in the multiple linear regression analysis, for each increase in the consumption of 2 (355 mL) soft drinks/d, the average change between baseline and follow-up HOMA-IR showed an increase of 1.11 units (95% CI: 0.74, 1.48).

Discussion

In the present prospective cohort study, we observed that soft drink consumption is associated with changes in HOMA-IR, regardless of known risk factors, including age, sex, smoking, educational level, alcohol intake, physical activity, and family history of diabetes. In addition, our results suggest no significant association between diet soda and changes in HOMA-IR. Therefore, our data suggest that regular soft drink intake, but not diet soda consumption, is associated with increased levels of HOMA-IR, which could be related to increased risk of T2D and other chronic conditions in our population.

Several observational studies (23, 25, 26, 34, 36) and clinical trials (18, 37, 38) have explored the association between soft drink consumption and risk of IR (HOMA-IR). However, the results of the observational studies have been contradictory, with some of them finding no association (25, 26) and others observing a positive relation (23, 34, 36). With respect to randomized clinical trials (18, 37, 38), although these found positive results and provided the most consistent causal evidence, they only evaluated short-term effects, and the regulation of SSB intake that occurred in these studies did not reproduce all cultural, social, and other lifestyle factors influencing SSB consumption and its metabolic effects (39).

A recent study by Ma et al. found an association between higher SSB intake and a greater increase in HOMA-IR, which is consistent with our results. It is important to highlight that, in the study by Ma et al. (34), the highest SSB consumers had a median intake of 6 servings/wk, while in our population the median intake was 7.3 servings/wk. Also, Lana et al. (40) published a study conducted in Spain, in which they observed that, for men, a 1-serving (200 mL)/d increase in the consumption of SSBs was associated with higher plasma concentrations of insulin (2.14%, $P = 0.01$) and higher HOMA-IR (1.90%, $P = 0.04$). Also, in the Framingham Offspring Study, participants with intakes of ≥2 portions/d of SSBs were linked to higher insulin concentrations and HOMA-IR (23).

The association between soft drink intake and IR or HOMA-IR levels has been attributed to multiple factors, including the following: higher caloric consumption, the high sugar content in soft drinks (especially high-fructose corn syrup), less satiety and incomplete compensation for total energy at subsequent meals after calorie intake from liquids, and a broad influence of refined-carbohydrate intake, perhaps explained by their high glycemic index (41). Moreover, other nonphysiological factors, such as dietary behavior and the economics of food choices, have been associated (42). In this sense, for example, greater intakes of added sweeteners, which are rapidly absorbed, such as high-fructose corn syrup (the main sweetener in soft drinks), can lead to IR through weight gain, inflammation, and β-cell dysfunction (8, 15). Supporting this pathway, previous reports have suggested that these sweeteners have lower satiety than solid foods containing the same quantity of calories and their intake increases appetite, which may lead to excessive energy intake and increased adiposity and promote liver fat deposition, encouraging impaired insulin sensitivity and IR (41). Finally, it has been documented that dietary behaviors among subjects with a high intake of soft drinks show a pattern characterized by higher intakes of calories, saturated fats, and *trans* fats and lower consumption of fiber and a sedentary lifestyle, which could be related to metabolic abnormalities including IR (43). In this sense, previous studies have reported that a dietary pattern characterized by a high consumption of soft drinks, burgers and sausages, crisps, other snacks, and white bread and a low consumption of whole-grain bread was positively related to IR

(44). However, further work is required to evaluate the effect of soft drink consumption as part of specific dietary patterns.

One of the main strengths of our prospective study is the comprehensive dietary, lifestyle, and clinical data assessment using validated instruments. The HWCS is a study with long-term repeated assessment of diet, which allows us to compute the cumulative consumption of soft drinks. Another methodological strength is that we performed 2 sensitivity analyses. In this sense, we excluded incident glucose-intolerant and diabetes cases with the idea that this would rule out the possibility of reverse causation, given the fact that subjects with a new diagnosis might change their soda consumption; and second, we considered adjustment for well-measured confounders, such as energy intake, dietary patterns, and BMI, in order to be consistent with previous analyses.

Among the limitations, our study is mainly composed of health workers and their relatives who live in central Mexico and who are middle class, which may limit the generalizability of our results to other groups. Even though we adjusted for multiple potential confounders (e.g., dietary and lifestyle factors), residual confounding cannot be ruled out due to the observational nature of the present study. Measurement errors when evaluating dietary intake from an FFQ are inevitable; confounding due to unmeasured dietary items (e.g., amount of sugar) can also occur. Despite this fact, this error would translate into attenuated estimates, so we assume that the associations observed without these errors would be even greater. However, it has been reported that, for most nutrients, means estimated by the FFQ were within 10% of the food records or diet recalls, and the correlation between the FFQ and the records and recalls was similar to other FFQs (27, 28). The time between each measurement is another limitation, as well as the low level of consumption of soft drinks in our population (compared to the national average), which might be related to high educational level and awareness.

Overall, our data support the hypothesis that, in Mexican adults, a higher soft drink consumption is associated with changes in HOMA-IR. These findings support the need for reinforcing the policies to reduce soft drink consumption in our population.

The authors' responsibilities were as follows—RV-C, ED-G and JS: designed the research; BR-P, ED-G, JS, and PR: conducted the research; TB-G, BR-P, ED-G, RH-L, LL-M, and PR: provided essential reagents or essential materials; BR-P, TB-G, LT-I, and RG-M: analyzed data or performed statistical analysis; ED-G and BR-P: wrote the manuscript; and all authors: reviewed the manuscript, had primary responsibility for final content, and read and approved the final manuscript. The authors report no conflicts of interest.

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